FATAL ACUTE FIBRINOUS AND ORGANIZING PNEUMONIA IN A CHILD WITH JUVENILE DERMATOMYOSITIS

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Acute fibrinous and organizing pneumonia, a recently described form of diffuse acute lung injury, sometimes affects adults with inflammatory myopathy. We describe a child with juvenile dermatomyositis who had development of acute fibrinous and organizing pneumonia. There does not appear to be a successful method of treatment, particularly in severe cases with respiratory failure. ***(J Pediatr 2005;146:289-292)***

Juvenile dermatomyositis (JDM) is an uncommon disease of childhood. Acute pulmonary disease is known to occur in adult dermatomyositis, but it is not well described in JDM. A histologic pattern of acute lung injury termed acute fibrinous and organizing pneumonia (AFOP) has recently been described in adults and appears to be particularly associated with inflammatory myopathies.[1] AFOP is a form of acute lung injury and possibly a variant of diffuse alveolar damage (DAD). We describe a fatal case of AFOP in a child with JDM and review other reports of acute lung injury in JDM.

CASE REPORT

A 14-year-old Hispanic girl was evaluated because of a photosensitive rash, joint pain, and muscle weakness. She had been treated with 3 weeks of prednisone therapy for possible systemic lupus erythematosus. She was born at 28 weeks' gestation and underwent 1 month of care in the neonatal unit but subsequently was healthy without a history of bronchopulmonary dysplasia, reactive airway disease, or other respiratory symptoms. Her mother died at 24 years of age from complications of systemic lupus erythematosus. Examination revealed Gottron papules, heliotrope rash, and a rash over the left cheek, pinnae, neck, and forearms. Musculoskeletal examination revealed proximal muscle weakness, diffuse muscle tenderness, and symmetric polyarthritis.

Laboratory testing revealed elevation of some muscle-derived enzymes, von Willebrand factor antigen, and positive antibody to nuclear antigen (Table I). The chest radiogram was normal. Electromyography revealed extensive myopathic changes. JDM was diagnosed on the basis of the characteristic rash, weakness, elevated muscle-derived enzymes, and electromyographic findings.

Prednisone (30 mg prednisone bid, 1 mg/kg) and naproxen were begun. Over the next 8 weeks, rash, arthritis, and strength improved, but she had development of steroid-induced hyperglycemia and was started on insulin and metformin. Methotrexate was added as a steroid-sparing agent. She received 2 weekly doses of 10 mg (6 mg/m^2) and a dose of 15 mg (8.9 mg/m^2). This was stopped because aspartate aminotransferase and alanine aminotransferase remained abnormal and gamma glutamyl transferase (GGT) was elevated. Over the next 10 weeks she had development of cutaneous ulcerations. Hydroxychloroquine was added.

Two weeks later she had acute dyspnea. Computed tomography revealed extensive parenchymal process with patchy densities prominent in both lower lobes. An atypical pneumonia was diagnosed. She was treated with azithromycin and increased doses of corticosteroids. Four days later she was transferred to our institution, with persistent hypoxemia. On day 6 of her illness, bronchoalveolar lavage (BAL) was performed; testing for infectious pathologies, including *Pneumocystis jeroveci* (previously *carinii*), respiratory viruses, *Mycoplasma*, fungi, and bacteria was negative. Blood, BAL, and tissue cultures were

AFOP	Acute fibrinous and organizing pneumonia	IP	Interstitial pneumonitis
BAL	Bronchoalveolar lavage	JDM	Juvenile dermatomyositis
DAD	Diffuse alveolar damage		

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Table I. Results of relevant laboratory evaluation

Variable	Visit 1	HD 7	HD 11	HD 19	Normal
*AST	205				(10–30 U/L)
*ALT	192				(5–35 U/L)
*LDH	956				(380–640 U/L)
CK	50				(50–295 U/L)
Aldolase	10.8	16			(3–12 U/L)
*von Willebrand factor antigen	428		357		(46%–142%)
ESR	16				
CBC	WNL	WNL			
Electrolytes	WNL				
Glucose	WNL				
*ANA	1:160-speckled	NEG			
Complements	WNL	WNL			
Scl-70, RNP, SS-A, SS-B, Smith	NEG	NEG			
Anti-cardiolipin antibodies	NEG				
Lupus anticoagulant	NEG				
Anti-ds DNA		NEG			
Anti-LKM		NEG			
Mitochondrial M2		NEG			
Jo-1		NEG			
Anti-smooth muscle		NEG			
ANCA		NEG			
Hepatitis A antibody		NEG			
Hepatitis B antibody, HBsAg		NEG			
Hepatitis C antibody		NEG			
Epstein-Barr virus IgM, PCR		NEG			
Legionella DFA, culture, PCR			NEG		
Bartonella IgG, IgM			NEG		
Chlamydia IgG, IgM			NEG		
Chlamydia culture			NEG	NEG	
Parvovirus PCR				NEG	
Cytomegalovirus Buffy coat DIF		NEG			

Abnormal results (*) are presented, with normal values in parentheses.
HD, hospital day; *WNL*, within normal limits; *NEG*, negative; *DIF*, direct immunofluorescence; *PCR*, polymerase chain reaction.

negative for bacterial, fungal, and mycobacterial organisms. She received 3 consecutive days of methylprednisolone (1 g/d) and intravenous immunoglobulin (2 g/kg) without improvement. Video-assisted thoracoscopic surgical lung biopsy revealed AFOP (Figure). Special stains for infectious organisms (acid-fast bacillus, Grocott methenamine silver, Warthin Starry, tissue Gram stain, and immunohistochemical stains for cytomegalovirus, adenovirus, and herpesvirus types I and II) were performed, all with negative results.

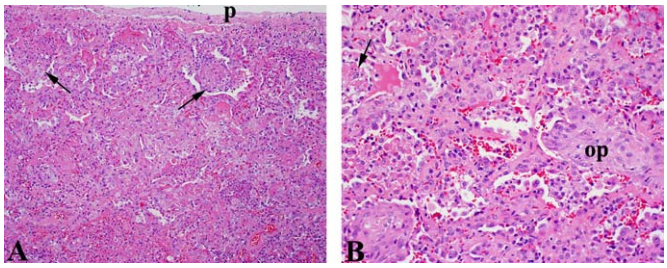

Figure. Acute fibrinous organizing pneumonia. Scanning magnification view (**A**) of lung biopsy shows diffuse pattern of acute lung injury extending to involve the pleura (*p*). A proportion of the original patients described with AFOP had similar diffuse parenchymal involvement (*1*). Alveolar spaces are not readily visible given extensive filling by pink fibrinous exudates. Mild chronic inflammatory infiltrate (lymphocytes and plasma cells) is present in the interstitium, imparting a slightly blue appearance to the background lung tissue. At higher magnification (**B**), the essential elements of the diagnosis become apparent, with patches of airspace organization (*op*) alternating with bright pink balls of organizing fibrin in the airspaces (*arrow*). No hyaline membranes were present. All special studies for infectious organisms on the biopsy material were negative (hematoxylin and eosin stain: **A,**original magnification, ×100; **B,**original magnification, ×200).

Needle biopsy of the liver showed mild steatosis. On day 7, *Mycoplasma* immunoglobulin M was positive (1.09 [negative or equivocal <0.95], but on day 11, both culture and polymerase chain reaction for *Mycoplasma* was negative on the lung biopsy tissue. Other laboratory tests were unrevealing (Table I).

She was treated with azithromycin, but the respiratory failure worsened over the next 5 days, with increased oxygen requirements and dyspnea. A repeat BAL and extensive evaluation again failed to demonstrate an infectious agent. Intravenous cyclosporine was started at 5 mg/kg per day, and a dose of cyclophosphamide at 500 mg/kg was administered intravenously. She was placed on conventional and then oscillating mechanical ventilation but had persistent pleural air leak and massive subcutaneous emphysema. She died 2 weeks after admission to our institution.

Autopsy confirmed the diffuse acute pathologic process in the lungs, with edema, fibrinous exudates, hyaline membrane formation (not identified on initial biopsy), type 2 pneumocyte hyperplasia, and areas of organization. This evolution over time to a more classic DAD pattern was possibly a consequence of terminal events rather than a manifestation of the natural history of AFOP.

DISCUSSION

Juvenile dermatomyositis is characterized by vasculopathy of the skin and muscles, proximal muscle weakness, and typical skin rash. Pulmonary involvement has been reported less frequently in children with JDM than in adult patients. Abnormalities of pulmonary function in the absence of respiratory symptoms have been described in JDM, suggesting that subclinical involvement might be more common than is generally appreciated.[2,3] Several case reports describe the

Table 2. Comparison of acute and subacute diffuse lung disease patterns

	AFOP	DAD	COP	AEP
Mean age (y, range)	62 (33–78)	50 (7–77)	58 (21–80)	32 (18–64)
Duration of symptoms before diagnosis	19 d (2–60)	3–18 d	<3 mo	<7 d
Hyaline membranes	No	Yes	No	Sometimes
Extravascular eosinophils	No	No	No	Yes
CT findings	Bilateral bibasilar infiltrates; rarely, reticulonodular opacities	Bilateral infiltrates	Bilateral diffuse alveolar opacities, often peripheral, sometimes with irregular linear or nodular interstitial infiltrates	"Migratory" ground glass infiltrates
Therapy	No effective therapy identified	No effective therapy identified	High-dose systemic corticosteroid	High-dose systemic corticosteroid
Prognosis	Bimodal with 50% mortality correlating with severity	58% Mortality	12% Mortality	100% Survival
Reference	1	12	13	14

AFOP, acute fibrinous and organizing pneumonia; *DAD*, diffuse alveolar damage; *AEP*, acute eosinophilic pneumonia; *COP*, cryptogenic organizing pneumonitis (also known as idiopathic bronchiolitis obliterans organizing pneumonia).

occurrence of interstitial pneumonia (IP) and/or pneumothorax in JDM.[4-6] The IP in these cases was not well defined, and pneumothorax often dominated the presentation, sometimes with acute respiratory failure.

In 1975, Park and Nyhan[7] described a 12-year-old boy who had respiratory symptoms 4 months after the onset of JDM. Radiographs revealed bilateral basal infiltrates. He died after massive subcutaneous emphysema and pneumothorax. Histopathology of the lungs showed organizing DAD with proteinaceous exudates and hyaline membranes, expected findings for the organizing phase of DAD. His course was complicated by *Staphylococcus aureus* septicemia.

There are reports of fatal DAD in adults with dermatomyositis/polymyositis.[8-11] Tazelaar et al[8] reviewed lung biopsy specimens in patients with dermatomyositis/polymyositis and classified the observed IP into three groups: usual IP, bronchiolitis obliterans organizing pneumonia, and DAD. All three cases with DAD died after 1 to 6 weeks of respiratory failure. Lee et al[9] reported 5 patients with inflammatory myopathy and DAD. Despite intensive immunosuppressive therapy, all of them died. In a recent series, adults with AFOP who had respiratory failure requiring mechanical ventilation had a poor outcome, as did our patient.[1]

Dyspnea developed in our patient 4 months after the onset of JDM, while receiving high doses of prednisone and hydroxychloroquine. Therapy with high-dose methylprednisolone, cyclosporine, intravenous immunoglobulin, and cyclophosphamide was insufficient to treat the pulmonary process. The patient had received 3 doses of methotrexate (a described cause of lung toxicity) approximately 12 weeks before the onset of pulmonary symptoms, but the lack of typical changes on lung biopsy, absence of peripheral eosinophilia, and failure to improve with immunosuppressive therapy argue against methotrexate-induced pneumonitis as a contributing factor. It is possible but unlikely that *Mycoplasma* initiated her acute lung disease but was rapidly eradicated by treatment with azithromycin. It is unclear what role, if any, prematurity or metformin therapy played in the development of the pulmonary process.

All examples of acute lung injury (including DAD) invoke the same differential diagnosis: infection, drug reaction, systemic connective tissue disease with pulmonary manifestation (as in our patient), and an idiopathic form ("acute IP"). The lung reactions encompassed by the terms AFOP and DAD probably represent forms of acute lung injury existing along a spectrum related to severity and mechanism of injury (Table II).[12-14] AFOP describes a relatively distinctive pattern of acute lung injury (eg, edema, fibrin exudation, and diffuse pneumocyte injury) lacking the classic hyaline membranes of DAD and sometimes affecting the lung in a more patchy distribution. Both imply a potentially adverse prognosis.

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